REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.114, are respectfully requested in light of the following remarks.

This amendment accompanies a Request for Continued Examination (RCE) in compliance with 37 C.F.R. § 1.114; it is being filed together with a Petition for Extension of Time of one month and the requisite extension fee extending the period for response to the final rejection.

STATUS OF CLAIMS

Claims 1, 3-15, 20, 21, 23, 26, 27, 30-35 and 38 remain in this application. Claims 16, 29, 36 and 37 have been cancelled by the foregoing amendment, without prejudice or disclaimer. Claims 2, 17-19, 22, 24, 25 and 28 were previously cancelled.

Claims 1, 4, 5, 13, 14, 30, 31 and 38 have been amended hereinabove.

DISCUSSION OF CLAIM AMENDMENTS

Claim 1 has been amended to incorporate therein the feature of previously presented Claim 37, which has been cancelled as redundant. The organogelling substance of the composition of Claim 1 is now selected from the group consisting of N-lauroyl-L-alanine methyl ester, N-lauroyl-L-alanine ethyl ester, N-stearoyl-L-alanine methyl ester and N-stearoyl-L-alanine ethyl ester, which is supported at least by page 12, lines 24-30, of the as-filed specification.

Claims 4, 5, 13 and 14 have been slightly revised so as to use language which has a proper antecedent basis in Claim 1.

Claims 16 and 29 have been cancelled because they contained broader language than is present in amended Claim 1.

Claims 30 and 31 have been amended to depend from Claim 1 rather than from cancelled Claim 29.

Claim 36 has been cancelled because it contained broader language than is present in amended Claim 1.

Claim 37 has been cancelled as redundant because its definition of the organogelling substance has been incorporated into Claim 1.

Claim 38 has been amended to depend from Claim 1 rather than from cancelled Claim 37.

It is apparent from the foregoing that no new matter has been introduced by these claim amendments.

CLAIM REJECTIONS - 35 U.S.C. § 103(a)

Claims 1, 3-16, 20, 21, 23, 26, 27 and 29-38 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Fanara et al. U.S. Patent No. 6,464,987 in view of El-Nokaly et al. U.S. Patent No. 5,843,407. Applicants submit that this newly made rejection is untenable against the claims now in this application and should be withdrawn.

The subject matter of Claim 1 of the present application, which is the only independent claim herein, is a heat-sensitive composition in liquid form, comprising

- a hydrophobic organic liquid,
- an organogelling substance which is selected from the group consisting of N-lauroyl-L-alanine methyl ester (LAM), N-lauroyl-L-alanine ethyl ester (LAE), N-stearoyl-L-alanine methyl ester (SAM) and N-stearoyl-L-alanine ethyl ester (SAE),

the molecules of which have the capacity to bind together via bonds of low energy, and

- a bioactive substance,

which changes to the organogel form during its administration to an animal body and remains in gel form at the body temperature of said animal body.

Hence, the composition of the invention is under liquid form, and not under a gelled form, although it contains "an organogelling substance". This is due to the fact that said organogelling substance chosen in the invention is "heat-sensitive," i.e., changes from the liquid state to the gel state as a function of the temperature (page 1, lines 25-26 of the original specification). Hence, the gelation of the liquid composition can be induced by cooling the site of application of the composition (page 9, lines 2-5 of the original specification). See also page 21, which describes at lines 24-35, how the composition is liquid at room temperature, is injected, then the injection site is immediately cooled to allow *in situ* gelation; after gelation is complete, the cooling system is removed, the site of injection returns to body temperature and the organogel remains stable at that temperature. This then affords delivery over time, such as a day or week.

Fanara et al. also disclose fluid pharmaceutical compositions for controlled release of active substance. However, these compositions contain phospholipids as organogelling substances. Fanara et al. do not teach any organogelling substance which is an amino acid derivative, much less one of the four specific compounds LAM, LAE, SAM and SAE.

Furthermore, the compositions taught by Fanara et al. are not heat-sensitive because they are able to gellify *in situ* by absorption of the surrounding physiological fluids. Contrary to what the Examiner proposes, Fanara et al.'s compositions will not have a transition temperature from liquid to gel lower than the temperature of the site of the injection; that is, cooling Fanara's compositions will certainly not result in their gellification, since the gellification process of Fanara et al.'s compositions relies on *in vivo* absorption of fluids and not on changes in temperature. On the contrary,

cooling the "heat-sensitive" composition of the present invention triggers its gellification (cf. Figure 1, for example, of the as-filed specification) as explained above. Moreover, even assuming for the sake of argument that body temperature (which is higher than room temperature) causes Fanara et al.'s fluids to gellify under the skin or muscle, then Fanara et al.'s compositions would act in the opposite way from those of applicants', which are cooled in order to gellify. However, Fanara et al. clearly teach, for example, in column 5, lines 18-26, that their compositions gel instantaneously in the presence of an aqueous phase; this does not evidence sensitivity to heat.

Thus, a man skilled in the art could not follow Fanara et al.'s teaching in order to realize the present invention.

To have the idea to use LAM, LAE, SAM or SAE as the organogelling substance in their composition, the present inventors had to know that LAM, LAE, SAM and SAE:

1) are compatible with *in vivo* administration,

2) are heat-sensitive components (i.e. liquid at room temperature to be injectable and gellified after cooling to form an implant), and

3) can liberate bioactive substances.

None of these elements have been described or even suggested by El-Nokaly et al., the secondary reference.

As a matter of fact, the El-Nokaly et al. patent relates to lipstick compositions which comprise a gelling agent selected from the group consisting of hydrophobic silicas, hydrophobic clays with an effective amount of an activator, propylene carbonate, ethyl cellulose, n-acyl amino acid amides and n-acylamino acid esters and mixtures thereof. (col. 5, lines 10-14). The N-acyl amino acid derivatives are taught to be prepared from glutamic acid, alanine, lysine, glutamine, aspartic acid and mixtures thereof, (col. 7, lines 41-47). Preferred gelling agents are taught to be n-acyl glutamic acid amides and n-acyl glutamic acid esters of a particular structure (col. 7, lines 45-62). The patent goes on to name a number of specific gelling agents

of this type, which are referred to as preferred secondary gellants (col. 7, line 64 to col. 8, line 14). Every specific gelling agent named there is an amide of glutamic acid. The only specific gelling agent of this type exemplified in the patent is N-lauroyl-L-glutamic acid-di-n-butyl amide, which is named as the gelling agent in Examples VII and VIII. Applicants' claims now require a gelling agent selected from LAM, LAE, SAM and SAE. The cited El-Nokaly et al. patent neither discloses nor suggests any specific alanine ester derivatives, much less these four compounds. Moreover, the man skilled in the art only learns from El-Nokaly et al. that N-acyl amino acid derivatives generally can be gelling agents. However, this feature was already disclosed in several other documents previously quoted by the Examiner, in particular in Luo et al.

El-Nokaly et al. neither teach nor suggest that LAM, LAE, SAM or SAE is compatible with *in vivo* administration. The presence of amino acid derivatives in a lipstick composition does not mean that it is safe to be incorporated in a composition dedicated to be administered *in vivo* by injection.

Moreover, it is not taught or suggested by El-Nokaly et al. that LAM, LAE, SAM and SAE are liquid at room temperature and gellify when cooled. Indeed, lipsticks are solid compositions at room temperature, which is due to the high content of wax present in lipstick compositions (40% to 60%) and not to the 2% of amino acid derivatives potentially present in the composition. El-Nokaly et al.'s gelling agent is intended to facilitate the retention of emollient oils in lipstick compositions, especially at high humidity and high temperatures. It has nothing to do with compositions which can be cooled after injection in order to gellify *in vivo* and provide sustained release of bioactive substances.

In particular, El-Nokaly et al. do not teach the behavior of any amino acid derivatives, far less LAM, LAE, SAM or SAE, inside the body. It is therefore not obvious that a composition by virtue of the fact that it contains LAM, LAE, SAM or SAE, after being cooled so as to form a gel following injection in liquid form, will remain in gel form at body temperature as the present composition does.

As noted before, El-Nokaly et al. teach that the inclusion of their gelling agent facilitates the retention of emollient oils particularly under high humidity and temperatures (Abstract). For example, 2% of N-lauroyl glutamic acid di-n-butyl amide is able to provide a lipstick which is sweat-resistant or sweat-free (Examples 7 and 8 and col. 25, lines 13-18), that is, which avoids the excretion of oils on to the surface of the lipstick. Hence, the El-Nokaly et al. patent does not teach the use of any amino acid derivatives, much less LAM, LAE, SAM or SAE, to facilitate the release of bioactive substance.

Thus, El-Nokaly et al. combined with Fanara et al. do not teach or suggest the essential features required to realize the present invention, which is therefore not obvious. it was not obvious from these references separately or in combination that LAM, LAE, SAM and SAE were: (1) compatible with *in vivo* administration, (2) heat-sensitive, and (3) efficient for sustained release of active substance.

The rejections of the instant claims under 35 U.S.C. § 103(a) are thus without merit and should be withdrawn. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

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